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Citation

Mueller, Nancy. 1995. Overview: viral agents and cancer. Environmental Health Perspectives 103(Suppl 8): 259-261.

Published Version

doi:10.2307/3432322

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Overview: Viral Agents and Cancer

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Substantial evidence indicates that several common viruses are clearly or probable causal factors in the etiology of specific malignancies. These viruses either normally establish latency or can become persistent infections. Oncogenesis is probably linked to an enhanced level of viral activation in the infected host, reflecting heavy viral dose or compromised immune control. The major virus-malignancy systems include hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma (ATL); Epstein-Barr virus (EBV) and endemic Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's disease; and human papilloma virus (HPV) and cervical cancer. Of these, a vaccine is available only for HBV. These malignancies tend to occur in early to mid-life and account for a substantial amount of morbidity and person-years lost. They are also likely to occur as "opportunistic malignancies" among individuals infected with human immunodeficiency virus type-1, particularly among those who experience prolonged survival. — *Environ Health Perspect* 103(Suppl 8):259-261 (1995)

Key words: virus, cancer, HTLV-I, HBV, HCV, EBV, HPV

Introduction

Substantial evidence indicates that several common human viral infections clearly or probably are factors in the etiology of specific malignancies. The evidence for these relationships is aided by the revolution in molecular biology, resulting in more sensitive and specific assays for detection of viral genes or gene products. The evidence regarding causality is strongest when viral biomarkers are consistently identified in tumor tissue, particularly when clonality of viral sequences can be established. Identification of consistent alterations in the pattern of antibody response to viral antigens is also a useful strategy. Antibodies tend not to provide immunologic control to these viral infections; rather, in many cases elevated antibodies reflect a heavy viral or proviral load (1).

These viruses include the hepatitis viruses hepatitis B virus (HBV) and hepatitis C virus (HCV), human T-lymphotropic virus-type 1 (HTLV-1), Epstein-Barr

virus (EBV), and some human papilloma virus (HPV) genotypes that normally infect the genital tract. These viruses normally establish latency, or in the case of the hepatitis viruses, become persistent infections under certain circumstances. Risk of malignancy generally is related to some compromise to host control of the infection. This could be due to an early or severe primary infection or to a disruption of immune function such as that seen in human immunodeficiency virus-type 1 (HIV-1) infection. These malignancies generally are rare outcomes of these infections, which indicates that most individuals control these infections adequately.

The major virus-associated malignancies are listed in Table 1. These include a surprisingly diverse set of malignancies. The mechanisms involved are not understood. The simplest model of an insertion of viral sequences into a common, critical region of the host genome does not characterize any of these human virus-associated malignancies. Viral transactivation of host oncogenes is the most probable mechanism

in HTLV-1 (2). Several of these viruses have gene products that actually interact with suppressor genes, as is true for HPVs 16 and 18 (3). There may be less direct mechanisms of viral activity that increase the likelihood of chromosomal translocation leading to up-regulation of oncogenes such as in Burkitt's lymphoma (4). Alternatively, there may be a promoterlike mechanism by a recurrent induction of cell division, as seen in chronic HBV infection and hepatocellular carcinoma (5).

In general, these malignancies occur relatively early in life, typically peaking in middle-age or earlier, as shown in Figure 1. Such a curve indicates that risk is associated with infection in early life (10). This observation also implies that viral-associated malignancies have a disproportionate public health impact via years of life and working years lost.

The causal relationships between both HBV and HCV and hepatocellular carcinoma is established through substantial epidemiologic evidence (5). Both appear to act via chronic replication in the liver by causing cell death and subsequent regeneration. For HBV, the risk factor strongly associated with hepatocellular carcinoma is the seroprevalence of hepatitis B surface antigen (HBsAg), which is evidence of chronic viremia and occurs primarily under circumstances of perinatal infection, particularly among men. HBV-associated liver cancer almost always occurs in the presence of cirrhosis. The evidence for causality is the extremely strong association between the HBsAg and the evidence of integrated clonal HBV in tumor and surrounding tissue. After extensive review of the data, an International Agency for Research on Cancer (IARC) Working Group recently

This paper was presented at the President's Cancer Panel Conference on Avoidable Causes of Cancer held 7-8 April 1994 in Bethesda, Maryland. Manuscript received 9 March 1995; manuscript accepted 24 March 1995.

This research is supported in part by the National Cancer Institute grant R37-CA 38450.

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Abbreviations used: IARC, International Agency for Research on Cancer; HTLV-1, human T-lymphotropic virus-type 1; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HPV, human papilloma virus; HIV-1, human immunodeficiency virus-type 1; AIDS, acquired immunodeficiency syndrome; HBsAg, hepatitis B surface antigen; VCA, Epstein-Barr viral capsid antigen; IgA, immunoglobulin A; ATL, adult T-cell leukemia/lymphoma.

Table 1. The major virus-associated malignancies in humans.

Malignancy	Virus	Virus family
Hepatocellular carcinoma	HBV	<i>Hepadnaviridae</i>
Hepatocellular carcinoma	HCV	<i>Flaviviridae</i>
Adult T-cell lymphoma/leukemia	HTLV-1	<i>Retroviridae</i>
Burkitt's lymphoma	EBV	<i>Herpesviridae</i>
Nasopharyngeal carcinoma	EBV	<i>Herpesviridae</i>
Hodgkin's disease	EBV	<i>Herpesviridae</i>
Cervical cancer	HPV-16, 18, 31, 45	<i>Papovaviridae</i>

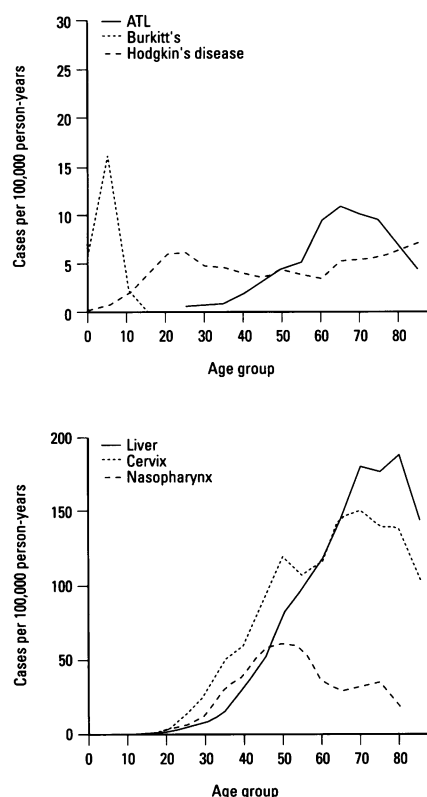


Figure 1. Age-specific incidence rates for the major virus-associated malignancies. Adult T-cell leukemia/lymphoma (ATL): males, 1986 to 1987, Kyushu, Japan (6); Burkitt's lymphoma: males, 1961 to 1975, West Nile District, Uganda (7); Hodgkin's disease: males, 1986 to 1990, SEER Program (8); nasopharynx: males, 1983 to 1987, Chinese, Singapore (9).

concluded that HBV is a Group I human virus-associated carcinogen. Intervention by immunization of high-risk infants, which is now under way in many endemic populations, is likely to prevent the disease among future generations. Treatment of chronic HBV infection with a combination of interferons has been found to be effective in converting patients from an antigenemia to an antibody-positive state (5).

In contrast to the long history of research on HBV, HCV has only been identified since 1989 (5). The virus itself has not even been visualized, although it has been cloned, and its natural history is largely undefined. Serologic and genome probes have been developed using cloned fragments of the virus. Based on these biomarkers, the epidemiologic evidence linking HCV infection to hepatocellular carcinoma is so strong that it also has been classified as a Class I human carcinogen by IARC. These assays are being used to screen the blood supply, which should

reduce the incidence of HCV infection. There is some evidence that a proportion of HCV carriers who have evidence of chronic hepatitis can clear the infection with treatment by interferon (5).

The association between HTLV-1 and adult T-cell leukemia/lymphoma (ATL) also is firmly established (11). Unlike the other oncogenic viruses found throughout the world, HTLV-1 is highly geographically restricted, being found primarily in southern Japan, the Caribbean, west and central Africa, and the South Pacific islands. Evidence for causality includes the monoclonal integration of viral genome in almost all cases of ATL in carriers. No oncogene activation is seen, but it is thought that part of the oncogenic process involves the up-regulation of the transactivating *tax* protein of the virus. Like HBV and liver cancer, the risk factors for HTLV-1-associated malignancy appear to be perinatal infection, high viral load, and being male sex (2).

Since perinatal transmission of HTLV-1 occurs primarily through infected lymphocytes in breast milk, screening mothers in endemic populations prior to delivery and discouraging breast-feeding is substantially reducing the occurrence of perinatal transmission. Breast-feeding for less than 6 months appears to be equivalent to total cessation in reducing infection, and consensus on public health policies should be sought. The risk associated with sexually acquired infection has not been defined (2).

There is a substantial amount of evidence that EBV is a causal factor in three quite different malignancies. These include Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's disease. In each case, there are consistent serologic and molecular patterns of EBV fingerprints associated with the specific malignancy (1,4). These are summarized in Table 2. The potential

for developing a vaccine against EBV continues to be an important issue.

The evolution of our understanding of the role of EBV in endemic Burkitt's lymphoma led to three milestones that serve as paradigms for virus-associated malignancies. These include identification and isolation of the virus itself from Burkitt's tumor; use of the prospective seroepidemiologic study to identify the antibody pattern, which can distinguish future cases of the disease; and discovery of the link between the characteristic chromosome translocation and the activation of *c-myc* (4).

Clonal EBV episomes are found in essentially all cases of endemic Burkitt's lymphoma, which is traditionally defined as occurring in tropical areas among children with holoendemic malaria. It appears that a combination of early EBV infection with the constant mitogenic stimulation of malaria on infected lymphocytes inducing gene rearrangements for immunoglobulin specificity can set off the chain of events leading to the activation of *c-myc*. A secondary event in a suppressor gene probably also occurs. EBV is also found in about 20% of cases of nonendemic Burkitt's lymphoma. It is important to note that EBV-negative tumors share the same chromosomal translocation. This illustrates the general principle that there can be multiple causal pathways to the same syndrome and, in this case, the same genetic lesions.

The prospective study undertaken in Uganda in the early 1970s, which involved serologic testing of 42,000 children, led to identification of 14 subsequent cases (12). Antibody analyses of specimens from these cases and matched controls determined that although essentially all the children were infected with EBV at initial screen, those cases that resulted in cancer had significantly higher titers against the viral

Table 2. The pattern of Epstein-Barr virus biomarkers in associated malignancies.

Marker	Burkitt's lymphoma	Nasopharyngeal carcinoma	Hodgkin's disease
Antibody			
VCA			
IgG	↑↑	↑	↑
IgA	—	↑↑	↑
IgM	—	—	↓
EBNA	—	—	↑↑
Early antigen			
Diffuse	—	↑ (IgA)	↑
Restricted	↑ ^a	—	±
Molecular			
Clonality	Yes	Yes	Yes
Latent phenotype	EBNA-1 only	EBNA2-, LMP1+	EBNA2-, LMP1+

^aPredictive of recurrence following treatment.

capsid antigen (VCA). In addition, the appearance of an antibody to the restricted form of the early antigen following treatment indicated a relapse.

EBV is also clearly involved in the etiology of undifferentiated nasopharyngeal carcinoma, especially among persons of southern Chinese origin (13). Again, clonal episomal viral genome is found in the tumor and a distinctive serologic pattern is found at diagnosis, including the presence of immunoglobulin A (IgA) against the VCA. Relapse is heralded by the reappearance or increase in IgA against the VCA and the restricted form of the early antigen. In affected tissue, EBV expresses a unique latent phenotype that differs from that seen in Burkitt's tumor. It currently is not clear how other risk factors for nasopharyngeal carcinoma such as ingestion of salted foods relate to EBV in the pathogenesis of this malignancy. In terms of prevention in high risk populations, screening for the presence of IgA has been used to detect early, treatable cases (13).

EBV has been linked to Hodgkin's disease by serology both following and

preceding diagnosis (4). Further, there is a consistent association of young adult Hodgkin's disease with risk factors that implicate the role of late primary infection with EBV. Recently the presence of clonal episomal EBV in the Reed-Sternberg cells has been demonstrated in about half of cases. In these cases, the latent viral protein expression is the same as that seen in nasopharyngeal carcinoma. It is presently unknown whether the serologic and risk factor data are internally consistent with the molecular data and whether EBV-negative Hodgkin's disease has a different etiology.

The relationship between genital HPV strains and malignancy is much less clear. Most research has focused on cervical cancer, where the epidemiologic evidence points to the role of a sexually transmitted infection. It is probable that HPV will eventually be determined to play a role in a range of other malignancies. Much of this lack of clarity probably reflects the unique biology of these highly cell-associated viruses, which have not been successfully grown in tissue culture or been found to elicit a notable antibody response (14).

Thus, currently the only strategy for identification is to use molecular probes, which requires tissue from both cases and controls and raises issues related to test performance (15). Recently, there has been some success in developing antibody assays (16). The accumulating data strongly suggest that these oncogenic viruses are part of the causal chain (17). Whether antiviral intervention in high-risk women may be of benefit is unknown. Since early infection appears to be important, behavioral intervention among young women and their sexual partners is likely to be protective.

Finally, an important modifier of risk for both EBV and HPV (and probably the other oncogenic viruses) is HIV-1 infection (18). This includes the high risk of non-Hodgkin's lymphoma (both EBV positive and negative), cervical cancer, and to a lesser extent, Hodgkin's disease as opportunistic malignancies. These observations emphasize the importance of immune control of these generally prevalent infections. Thus, primary prevention for HIV-1 infection, either through changes in sexual behavior or by vaccination, will also reduce the burden of virus-associated malignancy.

REFERENCES

1. Evans AS, Mueller N. Viruses and cancer: causal associations. *Ann Epidemiol* 1:71-92 (1990).
2. Mueller N, Blattner W. Retroviruses: HTLV. In: *Viral Infections of Humans: Epidemiology and Control*. 4th ed (Evans AS, Kaslow R, eds). New York:Plenum Publishers, in press.
3. Wong M, Gruber M. Viral interactions with the p53 gene in human cancer: NCI workshop. *J Natl Cancer Inst* 86:177-181 (1994).
4. Evans AS, Mueller NE. Malignant lymphomas. In: *Viral Infections of Humans: Epidemiology and Control*. 4th ed (Evans AS, Kaslow R, eds). New York:Plenum Publishers, in press.
5. IARC. Hepatitis Viruses. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol 59. Lyon:International Agency for Research on Cancer, 1994.
6. Tajima K, The T- and B-cell Malignancy Study Group and co-authors. The 4th nationwide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. *Int J Cancer* 45:237-243 (1990).
7. Williams EH, Smith PG, Day NE, Geser A, Ellice J, Tukei P. Space-time clustering of Burkitt's lymphoma in the West Nile District of Uganda: 1961-1975. *Br J Cancer* 37:109-122 (1978).
8. Miller BA, Ries LAG, Hankey BF, Kosary CL, Harras A, Deresa SS, Edwards BK, eds. *SEER Cancer Statistics Review: 1973-1990*. National Cancer Institute. NIH Publ No 93-2789. Bethesda, MD:National Institutes of Health, 1993.
9. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J, eds. *Cancer Incidence in Five Continents*. Vol 6. IARC Scientific Publications No 120. Lyon:International Agency for Research on Cancer, 1992.
10. Doll R. An epidemiologic perspective of the biology of cancer. *Cancer Res* 38:3573-3583 (1978).
11. Mueller N. The epidemiology of HTLV-1 infection. *Cancer Causes Control* 2:37-52 (1991).
12. de-Thé G, Geser A, Day NE, Tukei PM, Williams EH, Beri DP, Smith PG, Dean AG, Bronkhamm GW, Feoriro P, Henle W. Epidemiological evidence for causal relationship between Epstein-Barr virus and Burkitt's lymphoma from Ugandan prospective study. *Nature* 274:756-761 (1978).
13. de-Thé G, Ho JHC, Muir CS. Nasopharyngeal carcinoma. In: *Viral Infections in Humans: Epidemiology and Control*. 3rd ed (Evans AS, ed). New York:Plenum Press, 1991;737-768.
14. Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. *Epidemiol Rev* 10:122-193 (1988).
15. Schiffman MH, Scharzkin A. Test reliability is critically important to molecular epidemiology: an example from studies of human papillomavirus infection and cervical neoplasia. *Cancer Res (Suppl)* 54:1944s-1947s (1994).
16. Galloway DA. Papillomavirus capsids: a new approach to identify serological markers of HPV infection. *J Natl Cancer Inst* 86:474-475 (1994).
17. Schiffman MH. Recent progress in defining the epidemiology of human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst* 84:394-398 (1992).
18. Levine AM. AIDS-related malignancies: the emerging epidemic. *J Natl Cancer Inst* 85:1382-1397 (1993).